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Case report

Malignant myositis ossificans: occult gastric carcinoma presenting as an acute rheumatic disorder

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SUMMARY A patient developed ossifying skeletal muscle metastases from a primary gastric mucin-producing adenocarcinoma. The unusual nature of skeletal muscle metastases and the inflammatory-like syndrome associated with heterotopic ossification is reviewed. It is suggested that this case of 'neoplasm-induced post-traumatic myositis ossificans' may be caused by the interaction of local haemorrhage and thrombosis, mucin-producing tumour implants, and the presence of large quantities of gamma-carboxyglutamic acid, an amino acid associated with the calcification of bone matrix formation.

We report the case of a patient in whom ossifying skeletal muscle metastases from an occult gastric carcinoma led to his presentation with a rheumatic illness characterised by back, hip, and shoulder pain. No similar rheumatic illness has been previously reported in association with malignancy.[1] Although nearly 50 cases of heterotopic ossification associated with malignancy have been reported, the aetiology remains obscure.[2–4] However, the recent biochemical discovery of the vitamin-K-catalysed conversion of glutamic acid to gamma-carboxyglutamic acid (GLA) may be related to neoplasm-induced heterotopic ossification. Our patient affords us the unique opportunity of examining this proposed relationship between GLA and heterotopic ossification induced by neoplasia.

Case report

A 54-year-old white male policemen was admitted to Presbyterian-University Hospital for evaluation of back and thigh pain. He had been well until 5 weeks prior to admission, when he slipped backwards and fell on the ice. The following day he experienced lower back and right groin pain extending into his anterior thigh. Four weeks of bed rest and exercise therapy failed to improve his discomfort. The patient stated that the pain was most severe at night and in the early morning when at rest, and seemed to be more tolerable when he 'got up and worked it out'. He began to notice pain in his left groin also radiating into his anterior thigh.

General physical examination was normal. Examination of the back showed restricted forward flexion (60° from the vertical). Neurological examination was normal. Laboratory investigation was unremarkable with the exception of a raised erythrocyte sedimentation rate of 44 mm/h. The roentgenograms of the lumbosacral spine, pelvis, and hips showed minimal degenerative changes.

Ten days after his admission to hospital pain developed in his left shoulder. Diffuse tenderness of the soft tissues of the lower back, right and left groin, and adjacent thighs was then noted. One week later dramatic swelling, pain, warmth, and erythema of the left shoulder occurred, with marked tenderness laterally. Rotation of the hips became strikingly limited.

Roentenograms of the left shoulder revealed ossification in the soft tissue adjacent to the proximal humerus, suggesting the early development of post-traumatic myositis ossificans (Fig. 1). Further roentgenographic and computerised axial tomographic (CT) examination revealed calcification and soft tissue masses in the lumbar paraspinal muscles, right obturator foramen, and in muscles around the right

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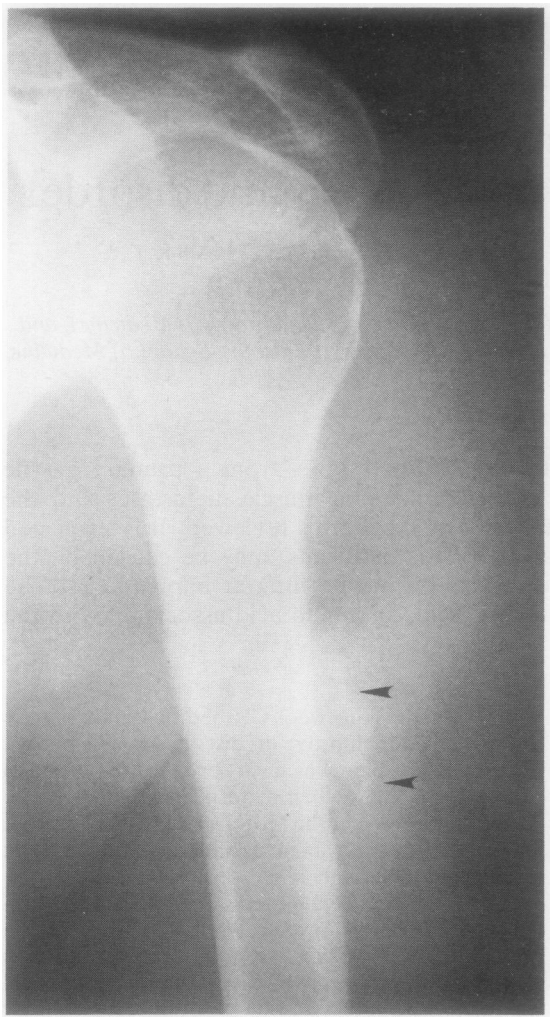

Fig. 1 *Left shoulder: ossification in soft tissues adjacent to humerus.*

and left femoral necks. Roentgenograms of those areas showed ossification. Biopsy of the soft tissue mass adjacent to the humerus revealed a mucin-producing adenocarcinoma with signet ring cell formation.

The patient became increasingly cachectic within the first 6 weeks of hospitalisation. He was begun on radiotherapy and chemotherapy with 5-fluorouracil. Although these treatments relieved his pain, his course was complicated by deep venous thrombosis, pulmonary embolus, and infarction. Bilateral ureteral obstructions occurred despite treatment. The patient died 2 months after admission. Autopsy showed the primary tumour to be an adenocarcinoma

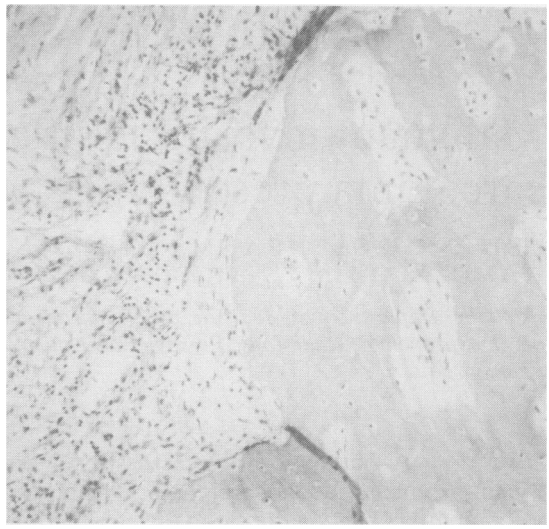

Fig. 2 *Metastatic carcinoma with adjacent heterotopic ossification.*

of the stomach, and a biopsy of the ossified soft tissue mass in the area of the right obturator foramen revealed metastatic carcinoma with adjacent heterotopic ossification (Fig. 2).

Discussion

Despite the large total mass and extensive blood supply of skeletal muscle, haematogenous metastases rarely develop within it. In one series of 500 autopsies of patients with various metastatic neoplasms only 4 examples of muscle metastases were described. These were associated with rapidly growing anaplastic cancers with numerous metastases in other tissues.[4] Not surprisingly, cases in which skeletal muscle metastases were the initial presentation of an occult neoplasm are similarly rare. In the 4 cases reported they presented as isolated enlarging muscle masses.[5-7] This striking resistance of skeletal muscle to implantation of haematogenous tumour emboli is not yet understood.

Our patient presented with the painful rheumatic disorder initially characterised by back and bilateral groin pain with radiation into his anterior thighs. A number of diagnoses were initially incorrectly considered. The development of a grossly inflamed shoulder was attributed to myositis ossificans. In addition the exacerbation of pain and stiffness at rest and in the morning, and improvement with activity, were early indications of what seemed an inflammatory illness. Goldberg and Schumacher have previously commented on the close resemblance

between acute arthritis and periarticular heterotopic ossification.[8] These sometimes dramatic symptoms seen both in benign heterotopic ossification and in our case are in contrast to the more bland appearance of nonossifying skeletal muscle metastases, and they suggest that neoplasm-induced heterotopic ossification may instigate apparently an inflammatory rheumatic syndrome.

The cause of neoplasm-induced heterotopic ossification remains unknown; however, we believe several observations are pertinent. Ossification occurs in direct contiguity with neoplasm, suggesting a local rather than a systemic osteogenic effect. Mesenchymal tissue with the ability to differentiate into osteoblasts must be locally available. Most cases of neoplasm-induced heterotopic bone formation have been reported in association with mucin-producing adenocarcinomas.[9] Although mucin has not been shown to have any osteogenic capability, it has been demonstrated to be thrombogenic, and the association between mucin-producing adenocarcinomas and venous thrombosis is well-recognised.[10]

Recently a relationship has been demonstrated between the coagulation protein prothrombin and the most abundant noncollagenous bone protein osteocalcin. Both proteins are enriched with GLA, an amino acid which is converted from glutamic acid by carboxylation, catalysed by vitamin K. GLA binds calcium with 10 times greater avidity than glutamic acid, making calcium locally available to activate prothrombin and probably to interact with osteocalcin in bone formation.[11] Experimental deficiency of vitamin K has been shown to inhibit normal bone formation, presumably owing to lack of formation of GLA.[12] We measured the level of GLA in serial 24-hour urine samples before and after treatment of this patient. These levels were elevated initially and fell after treatment (Table 1). GLA was thus present in large quantities and available for binding calcium both for thrombosis and matrix calcification.

Table 1 *24-hour urinary GLA determinations* (μmol/g creatinine)*

Before chemoradiotherapy	69·4
1 week after chemoradiotherapy	33·6
1 month after chemoradiotherapy	12·3

*Normal 24-hour urine GLA is < 40·5.

Trauma and secondary haemorrhage within muscle can be followed by post-traumatic myositis ossificans. However, the remarkable infrequency of myositis ossificans following muscular trauma suggests that individual host factors contribute to permitting or preventing its development. We suggest that hypercoagulability may be one such promoting factor. It is possible that our patient had a haematoma in the injured muscles after his fall. This haematoma may have breached his skeletal muscles' innate resistance to blood-borne tumour emboli. Once established, the metastatic mucin-producing tumour may have exerted a further tendency to thrombosis and clot formation by locally sequestering GLA and calcium. The host tissue skeletal muscle provided the mesenchymal cells which were then stimulated to form bone.

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